Docket No.: 273012012500
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: H. Andrew STRONG et al.	
Application No.: 10/072,272	Confirmation No.: 1974
Filed: February 6, 2002	Art Unit: 1617
For: PHOTODYNAMIC THERAPY OF OCCULT AGE-RELATED MACULAR DEGENERATION	Examiner: Y. S. Chong

APPELLANT'S BRIEF ON APPEAL

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

The rejection of claims 1, 2 and 5-20 is hereby appealed. This Brief is filed in accordance with 37 C.F.R. § 41.37.

A Notice of Appeal was filed in the present application on 14 October 2008, along with a Pre-Appeal Brief Request for Review. A decision stating that there were still appealable issues with respect to the appealed claims 1, 2 and 5-20 was mailed 10 November 2008. Thus, the due date for filing of a Brief remained 14 December 2008. A petition for an extension of time of two (2) months until 14 February 2009 is enclosed along with the required fee. Because 14 February 2009 fell on a Saturday, this Brief is filed on the next business day, Tuesday, 17 February 2009.

1. Real Parties in Interest

The Real Parties in Interest are the assignees herein, QLT Inc., having an address at 887 Great Northern Way, Vancouver, BC V5T 4T5, Canada, and Novartis, A.G., having an address at Lichtstrasse 35, 4056 Basel, Switzerland.

2. Related Appeals and Interferences

Appellants and their representatives and assignees are unaware of any proceedings related to, directly affecting, or that would be directly affected by or have a bearing on the Board's decision in this case.

3. Status of Claims

The application was originally filed with 21 claims. Claims 3 and 4 have been canceled. Claim 21 is withdrawn. Claims 1-2 and 5-20 have been finally rejected and are on appeal.

4. Status of Amendments

No amendments to the claims were proposed after final rejection.

5. Summary of Claimed Subject Matter

The invention is directed towards photodynamic therapy (PDT) methods for treating a sub-population of occult choroidal neovasculature (CNV) subjects having either or both of a small lesion or poor visual acuity prior to treatment (paragraphs 14-18).

CNV in wet age-related macular degeneration (AMD) can be generally divided into two forms, termed classic CNV and occult CNV, which are distinguishable by angiography (paragraph 4). A CNV lesion may be comprised only of occult CNV or may comprise both classic and occult CNV components (paragraph 5). A lesion in which the area of classic CNV occupies at least 50%

of the entire lesion (i.e., ≥50% classic) may be termed "predominantly classic" (paragraph 5). A lesion in which the area of classic CNV occupies more than 0% but less than 50% (i.e., the area of occult CNV is >50% and <100%) may be termed "minimally classic" (paragraph 5). "Occult lesions" refer to CNV lesions having an occult CNV component preferably comprising 50% to 100% of the lesion, and lesions defined as minimally classic that have an occult component (paragraph 12). While not all of these terms are explicitly required by the claims, an explanation of the terminology is provided to inform the discussion.

The present claims relate to methods of treating a specific sub-population of subjects (paragraph 13, last sentence) having occult CNV lesions, specified in the claims as subjects having an occult CNV lesion comprising an occult component of >50% and <100% of the lesion (paragraph 12). The same population may be referred to by reference to the percent classic CNV as having a lesion area composed of >0% to <50% classic CNV. Subjects are further assessed as having either or both (a) a small lesion, or (b) poor visual acuity (paragraph 19).

Small lesions are described as generally smaller than about 5 disc areas (paragraph 42). The lesion size must be less than 5 disc areas (paragraph 42) and may be (claim 5) less than 4 disc areas (paragraph 26). Poor visual acuity prior to treatment generally means a best corrected vision of less than 65 letters on modified Early Treatment Diabetic Retinopathy Study (ETDRS) charts, corresponding to visual acuity of less than about 20/50 or worse (paragraph 13, with further explanation at Example 1). As specified in the claims, poor visual acuity must be less than 65 letters prior to treatment (paragraph 13).

Subjects may be assessed (claim 2) by determining the size of the lesion (paragraph 15) and/or determining the best corrected visual acuity of the subject (paragraph 16).

The occult CNV lesion may be (claim 6) in a subject afflicted or diagnosed with age-related macular degeneration (AMD) (Abstract).

Photodynamic therapy (PDT) must be provided to the subject (paragraph 19). The PDT methods may include (claims 7-15 and 19) administration of a photosensitizer (PS) (paragraph 35). The PS may be administered (claim 8) at a concentration ranging between about 2 to 8 mg/M^2 (PS/body surface area of subject) (paragraph 93), and may be administered (claim 9) at a concentration of 6 mg/M^2 (paragraph 93). The PS may also be administered (claim 19) at a concentration ranging between about 10 μg/kg to 100mg/kg body weight (paragraph 94).

The PS may be (claims 10-12) a green porphyrin (paragraph 44). The green porphyrin may be (claim 11) selected from BPD-DA, BPD-DB, BPD-MA, BPD-MB, EA6, and B3 (paragraph 48), and may be (claim 12) BPD-MA (paragraph 48), which is sometimes referred to as verteporfin (paragraph 52).

The PS may be coupled (claim 13) to a specific binding ligand (paragraph 87). The PS may also be formulated (claim 14) with a carrier (paragraph 87). The formulation may be (claim 15) selected from the group consisting of a liposome, emulsion, or aqueous solution (paragraph 87).

The PDT method may comprise (claim 16) irradiation with electromagnetic radiation containing wavelengths in the visible light spectra (paragraph 105), and may provide (claim 17) about 12.5 J/cm^2 to about 100 J/cm^2 (paragraph 101). The irradiation may occur (claim 18) between 5 to 30 minutes after administration of a photosensitizer (paragraph 106, and original claim 18).

A resulting loss of visual acuity may be (claim 20) less with treatment than without treatment (paragraph 163 and Table 2).

6. Grounds of Rejection to be Reviewed on Appeal

Claims 1, 2, 5-12, 14-18 and 20 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over the TAP Report 1, *Arch. Ophthalmol.* 1999; 117:1329-1345 (hereinafter "TAP Report 1").

The TAP Report 1 is said to report methods of administering verteporfin, a green porphyrin, to patients suffering from occult CNV. The Examiner asserts that the treatment group of 402 patients included at least 305 patients having evidence of occult CNV and at least 199 patients having visual acuity less than 53 letters, and thus at least about 100 patients in the treatment group must have had evidence of occult CNV and visual acuity of less than 65. The Examiner further contends that 259 patients in the treatment group appear to have a lesion size of less than 6 disc areas. The Examiner asserts that the population with occult CNV in the treatment group of the TAP Report 1 is the same as the claimed population, and that all methods steps of the claimed process are described, such that the invention is inherently achieved.

The TAP Report 1 is said to show a benefit from verteporfin therapy in patients with predominantly classic CNV (i.e., ≥50% classic CNV) and in patients with no classic CNV (i.e., 100% occult CNV). The Examiner contends that routine experimentation would suggest the treatment of patients having occult CNV lesions with an occult component of >50% and <100% of the lesion. The TAP Report 1 is said to only fail to explicitly state that patients in the treatment group had an occult component of >50% to <100% of the lesion.

Claims 13 and 19 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over the TAP Report 1 in view of Zeimer (US 5,935,942). Zeimer is said to report the same process as the TAP Report 1, using a photosensitizer that is encapsulated or coupled with a targeting or tissue-

specific agent. The Examiner contends that Zeimer employs targeted liposomes, so that the inclusion of a targeting agent such as an antibody with the photosensitizer in the TAP Report 1 is allegedly suggested by combination of the TAP Report 1 with Zeimer. The optimization of the dosing range of the photosensitizer based on the subject's body weight is said to be obvious with routine experimentation.

7. Argument

A. There is no *prima facie* case that claims 1, 2, 5-12, 14-18 and 20 are rendered obvious over the TAP Report 1

Claims 10-12 will be argued separately.

Claims 1, 2, 5-9, 14-18 and 20

The TAP Report 1 reports the one-year results of two, multicenter randomized clinical trials to determine the effects of photodynamic therapy with verteporfin on the risk of vision loss in patients with subfoveal choroidal neovasculature (CNV) caused by age-related macular degeneration (AMD). (See page 1339, Objective.) The TAP Report 1 demonstrates that PDT with verteporfin was ineffective in improving visual acuity outcomes in the subgroup of patients having lesions in which the area of classic CNV was greater than 0% but less than 50% of the lesion area (i.e., lesions having an occult component of >50% and <100% of the lesion area). (See page 1341, col. 2.) The TAP Report 1 is silent with respect to other characteristics within this subgroup, and provides no guidance that would lead to the selection of the claimed sub-population of patients having occult CNV lesions with an occult component of >50% and <100% of the lesion area in combination with small lesion size and/or poor visual acuity.

The TAP Report 1 provides baseline characteristics by treatment group for the entire study population, including the Lesion area composed of classic CNV (%), Number of letters read (visual acuity) in treatment eye, and the Area of lesion (MPS disc areas). (See pages 1334-1335, Table 2.) The patient selection criteria required that the patient's lesion have some evidence of classic CNV, but the lesion could include occult CNV. (See page 1330, col. 1, Patient Selection.)

As described in the TAP Report 1, while 305 patients in the verteporfin treatment group had some evidence of occult CNV, only 201 patients had a lesion composed of >0% to <50% classic CNV (i.e., >50% and < 100% occult CNV, as featured in the claims). (See page 1334, Table 2.) No correlation was provided between these patients and those having poor visual acuity and/or small lesion size. Thus, no evidence has been provided to demonstrate that the instantly claimed sub-population is inherently present among the patients in the verteporfin treatment group of the TAP Report 1. It is well settled law that "[t]o establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." MPEP § 2112 (IV). Inherency may not be established by probabilities or possibilities. MPEP § 2112 (IV).

The primary efficacy outcome of the TAP Report 1 was the proportion of verteporfin-treated eyes versus placebo eyes with fewer than 15 letters lost (approximately <3 lines of visual acuity loss) compared with baseline examination at 1 year after study entry. (See page 1333, col. 1, Outcome Measurements.) Subgroup analyses were undertaken for the primary efficacy outcome at the month-12 examination. (See page 1338, col. 1.) The subgroup analyses showed that lesion composition significantly affected the magnitude of treatment benefit. (See page 1341, col. 2, first full paragraph.) Predominantly classic CNV lesions (≥ 50% classic) showed a significant treatment

benefit, while lesions in which the area of classic CNV was greater than 0% but less than 50% (i.e., >50% and <100% occult, as claimed) achieved no visual acuity benefit with treatment (i.e., no difference in the proportion of cases with a loss of ≥15 letters). (See page 1341, col. 2, first full paragraph.)

The TAP Report 1 reports that for patients whose lesions had an area of classic CNV >0% to <50% (i.e., >50% and <100% occult), a virtually identical percentage of patients in the verteporfin treatment and the placebo groups experienced a loss of less than 15 letters in their visual acuity at 12 month (55.9% with verteporfin treatment v. 55.3% placebo, p=0.92). (See page 1340, Table 5, rows 3-4.) Thus, for these patients, PDT with verteporfin was no more effective than placebo in preserving visual acuity.

By comparison, in patients with predominantly classic lesions (i.e., ≥50% classic), verteporfin treatment is reported to significantly increase the number of patients with a loss of less than 15 letters (67.3% with verteporfin treatment v. 39.3% placebo, p<.001). (See page 1340, Table 5, rows 1-2.) While a significant treatment benefit was also reported in patients with no evidence of classic CNV (see page 1340, Table 5, rows 5-6), the number of patients in this subgroup was small and, as noted by the authors, the patients did not meet the eligibility criteria for the trials. (See page 1339, col. 2.)

When the entire study population in the TAP Report 1 was subgrouped by the absence or presence of any evidence of occult CNV lesions (but not further defined by percent occult composition), patients with any evidence of occult CNV showed only a modest treatment benefit on visual acuity (56.5% verteporfin treatment v. 51.6% placebo, p=0.33, with a loss of less than 15 letters). (See page 1340, Table 5, rows 7-10.) Secondary efficacy outcomes of the TAP Report 1

study included angiographic outcomes such as progression of CNV and size of the lesion. (See page 1333, col. 1, Outcome Measurements.) No major difference in the progression of occult CNV was observed between the verteporfin treatment and placebo groups for eyes with evidence of occult CNV at study entry (see page 1337, col. 2), although the entire lesion size was more likely to be less than 6 disc areas at 12-months for the treatment group. (See page 1342, col. 1.)

The TAP Report 1 concludes that PDT treatment with verteporfin provided no visual acuity benefit and no appreciable difference from placebo for patients whose CNV lesions had an occult component of >50% to <100%. (See page 1341, col. 2.) The TAP Report 1 recommends PDT with verteporfin for the treatment of patients with predominantly classic subfoveal CNV from AMD, especially when the lesion has classic CNV and no occult CNV. (See page 1344, col. 2, Conclusions.)

No rationale has been provided to suggest why one of skill in the art would choose to disregard a major finding of a multi-center clinical research study and attempt to treat patients having occult CNV lesions with an occult component of >50% to <100%, for whom the TAP Report 1 clearly states that PDT treatment is ineffective in improving visual acuity or slowing progression of occult CNV.

Moreover, in determining the differences between the prior art and the invention as claimed, "the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." MPEP § 2141.02 (II).

The essence of the present invention is the selection of a sub-population of occult CNV patients having lesions with >50% and <100% occult component, and including the additional criteria of small lesion size, or poor visual acuity, or both, for whom PDT treatment is surprisingly

beneficial. As noted above, the TAP Report 1 teaches that PDT is ineffective for patients having occult CNV with an occult component of >50% and <100% lesion area, as claimed. Nothing in the TAP Report 1 teaches or otherwise suggests criteria for the identification of a sub-population of these patients for whom PDT treatment would be effective. In particular, the TAP Report 1 provides no correlation between the percent occult character of the patient's CNV lesion and visual acuity or lesion size, and no guidance is provided that would lead to the selection of the claimed sub-population having poor visual acuity, or small lesion size, or both, in combination with occult CNV lesions having an occult component >50% and <100% lesion area. Thus, the TAP Report 1 provides neither a reasonable expectation of success nor any motivation to practice the instantly claimed methods.

Claims 10-12

Claims 10-12 require that the method comprises administration of a green porphyrin photosensitizer (PS) administered at a concentration of 6 mg/m^2. Claim 11 requires the selection of the green porphyrin photosensitizer from a group that includes BPD-MA (i.e., verteporfin), and claim 12 requires administration of BPD-MA.

The TAP Report 1 describes the administration of verteporfin, a green porphyrin photosensitizer, at 6 mg per square meter of body surface area. (See page 1329, col. 1, Methods.) As discussed above, the TAP Report 1 teaches that PDT with verteporfin under these conditions was ineffective at preserving visual acuity in patients having occult CNV lesions with an occult component of >50% and <100% lesion area, and provided no guidance that would lead to the selection of the claimed sub-population.

Claims 10-12 as a whole are nonobvious over the TAP Report 1 for the reasons stated above with respect to claims 1, 2, 5-9, 14-18 and 20. In particular, in view of the express teachings of the TAP Report 1, the treatment of a sub-population of occult CNV patients belonging to a subgroup for whom verteporfin treatment at 6 mg/m^2 body surface area was shown to be ineffective, using the same photosensitizer or a close analog administered at the same dosage would not reasonably be expected to prove beneficial. No rationale has been presented that would lead to the selection of the claimed sub-population for treatment under the instant conditions in view of the express teachings of the TAP Report 1.

B. There is no *prima facie* case that claims 13 and 19 are rendered obvious over the TAP Report 1 in view of Zeimer

Claims 13 and 19 will be argued separately.

Claim 13

The combination of Zeimer with the TAP Report 1 is cited as allegedly suggesting the inclusion of a targeting agent, such as an antibody, with the photosensitizer in the TAP Report 1. The optimization of dosing ranges of photosensitizer based on body weight is said to be obvious with routine experimentation.

As held by the Supreme Court in *KSR International v. Teleflex, Inc.*, 82 USPQ2d 1385 (S. Ct. 2007), in order to find obviousness, it must be found that there is some reason that the skilled practitioner would look to an additional document in order to make the invention.

The teachings of the TAP Report 1 are discussed above. Zeimer describes a method of treating vasculature, including CNV, by administering a heat-sensitive liposome that contains a tissue-reactive agent which is effective to cause chemical tissue damage and occlusion following

activation, followed by heating to release the liposome's contents. (See col. 3, lines 10-24.) Tissue-reactive agents may include photosensitive agents. (See col. 7, lines 2-6.) Aluminum phthalocyanine tetrasulfonate is described as an exemplary fluorescent dye and tissue-reactive agent (col. 17, lines 10-12), having advantages over other photosensitizing agents. (See col. 21, lines 57-63, and col. 17, lines 17-33.) Zeimer includes a blanket assertion that the methods described are useful for the occlusion of classic and occult CNV. (See col. 8, lines 46-49.) However, no data is provided in humans afflicted with CNV or a relevant animal model to support this assertion.

Claim 13 relates to a method of treating occult CNV lesions in the sub-population of subjects described above, having an occult CNV lesion comprising an occult component of >50% and <100% of the lesion and assessed as having a small lesion size, or poor visual acuity, or both, using a green porphyrin PS administered at a concentration of 6 mg/m^2, where the PS is coupled to a specific binding ligand.

First, in view of the teachings of Zeimer that aluminum phthalocyanine tetrasulfonate has advantages over other photosensitizing agents (see col. 17, lines 17-33), one of skill in the art would be unlikely to look to Zeimer to suggest modification of the green porphyrin photosensitizer in the TAP Report 1 with a specific binding ligand.

Moreover, Zeimer provides no guidance with respect to patient characteristics that are important for efficacy, such as lesion composition, visual acuity, or lesion size, let alone a combination of these characteristics. Nothing in Zeimer remedies the deficiencies in the alleged *prima facie* case of obviousness over the TAP Report 1 alone, as stated above with respect to all the pending claims, and thus the method of claim 13 as a whole is nonobvious over the TAP Report 1 in view of Zeimer.

Claim 19

Claim 19 relates to a method of treating occult CNV lesions in a sub-population of subjects described above, comprising administering a PS at a concentration ranging between about 10 μg/kg to 100mg/kg (PS/body weight of subject). No specific portion of Zeimer is cited as rendering claim 19 obvious in combination with the TAP Report 1. Rather, optimization of dosing range based on body weight is said to be obvious with routine experimentation.

A *prima facie* case of obviousness for claim 19 has not been established for the reasons stated above with respect to claims 1, 2, 5-9, 14-18 and 20 for the TAP Report alone. Neither the TAP Report 1 nor Zeimer, alone or in combination, would lead to the selection and treatment of the claimed sub-population of patients, and thus claim 19 as a whole is nonobvious over the cited art.

C. The methods of the invention provide unexpected results

The Appellant's disclosure demonstrates an unexpected and advantageous improvement in visual acuity in a sub-population of occult CNV patients having small lesion size or poor visual acuity prior to treatment, with an enhanced improvement in visual acuity for occult CNV patients having both of these additional characteristics. (See paragraphs 160-163.) For example, for subjects having occult CNV lesions, visual acuity prior to treatment of <65 letters and a lesion size less than or equal to 4 disc areas, a 43.8% difference between the verteporfin and placebo groups was observed in the percent of subjects losing less than 15 letters at 24 months after the PDT initial treatment. (See paragraph 163, Table 2, row 2.) By comparison, no improvement in visual acuity was achieved 24 months after verteporfin treatment for patients having occult CNV lesions, visual acuity ≥ 65 letters at baseline and a lesion size of greater than or equal to 4 disc areas; indeed,

verteporfin treatment appeared negatively correlated with visual acuity in these subjects. (See paragraph 163, Table 2, row 6.)

The cited art provides no teaching or other rationale to suggest that treatment of the claimed sub-population would prove beneficial. The efficacy of treatment in the claimed sub-population could not be predicted in view of the teachings of the TAP Report 1 that PDT is ineffective in patients having an occult component as claimed, coupled with the lack of information or other guidance regarding additional features that would render treatment beneficial for these patients.

D. Conclusion

The present invention provides methods for treating a sub-population of occult CNV patients falling within a group for whom the TAP Report 1 teaches that PDT treatment with verteporfin is ineffective. The recognition that a specific sub-population of patients can be beneficially treated is unexpected in view of the teachings in the cited documents. The TAP Report 1, alone or in combination with Zeimer, simply provides no guidance that would lead to the selection and treatment of the claimed sub-population, and the cited documents would not provide a person of skill in the art with either a reasonable expectation of success or any motivation or other rationale to practice the instantly claimed methods.

8. Claims Appendix

An Appendix containing a copy of the claims as currently pending is attached.

9. Evidence Appendix

This appendix contains the following documents:

TAP Report 1, *Arch. Ophthalmol.* 1999; 117:1329-1345

Zeimer, US 5,935,942

10. Related Proceedings Appendix

There are no related proceedings, therefore no Appendix is included.

The Assistant Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.17 that may be required by this Brief, or to credit any overpayment, to **Deposit Account No. 03-1952**.

Respectfully submitted,

Dated: February 17, 2009

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CLAIMS APPENDIX

1. (previously presented): A method for treating an occult choroidal neovascular (CNV) lesion in a subject comprising

selecting a subject with an occult CNV lesion comprising an occult component of >50% and <100% of the lesion and assessed as having either (a) a small lesion with a size less than 5 disc areas, or (b) poor visual acuity of less than 65 letters prior to treatment, or both (a) and (b); and

providing photodynamic therapy (PDT) to the subject having said CNV lesion.

2. (original): The method of claim 1 wherein said subject was assessed by determining the size of said lesion and/or determining the best corrected visual acuity of the subject.

3-4. (canceled)

5. (previously presented): The method of claim 1 wherein the small lesion has a size less than 4 disc areas.

6. (previously presented): The method of claim 1, wherein said occult CNV lesion is in a subject afflicted or diagnosed with age-related macular degeneration (AMD).

7. (original): The method of claim 1 wherein said PDT comprises the administration of a photosensitizer (PS).

8. (original): The method of claim 7, wherein the PS is administered at a concentration ranging between about 2 to 8 mg/m^2 (PS/body surface area of subject).

9. (original): The method of claim 8, wherein the PS is administered at a concentration of 6 mg/m^2.

10. (original): The method of claim 9, wherein the PS is a green porphyrin.

11. (original): The method of claim 10, wherein the green porphyrin is selected from BPD-DA, BPD-DB, BPD-MA, BPD-MB, EA6, and B3.

12. (original): The method of claim 11, wherein the green porphyrin is BPD-MA.

13. (original): The method of claim 10, wherein the PS is coupled to a specific binding ligand.

14. (original): The method of claim 7, wherein the PS is formulated with a carrier.

15. (original): The method of claim 14, wherein the formulation is selected from the group consisting of a liposome, emulsion, or aqueous solution.

16. (original): The method of claim 1, wherein said PDT comprises irradiation with electromagnetic radiation containing wavelengths in the visible light spectra.

17. (original): The method of claim 16, wherein the irradiation provides between 12.5 J/cm^2 and 100 J/cm^2.

18. (original): The method of claim 17, wherein said irradiation occurs between 5 to 30 minutes after administration of a photosensitizer.

19. (original): The method of claim 7, wherein the PS is administered at a concentration ranging between about 10 μg/kg to 100mg/kg (PS/body weight of subject).

20. (previously presented): The method of claim 1, wherein a resulting loss of visual acuity is less with treatment than without treatment.

21. (withdrawn): The method of claim 11, wherein the green porphyrin is EA6.

EVIDENCE APPENDIX

This appendix contains the following evidentiary material already of record:

1. TAP Report 1, *Arch. Ophthalmol.* 1999; 117:1329-1345

2. Zeimer, US 5,935,942